

REMARKS

The pending claims in this application are 1-15 and 40-42. Claims 1 and 40-42 were amended to include the term "nitric oxide" before "neutralizing agent" simply to clarify the claimed invention. No new matter is introduced with this amendment.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Version with markings to show changes made". Also attached is a clean copy of the claims which is appropriately captioned.

35 USC § 103(a) Rejection

The Examiner has rejected claims 1-15 and 40-42 under 35 USC § 103(a) over US Patent No. 5,723,127 (Scott) in view of Fecho *et al.* 1994 *J. Immunol.*, 152:5845. The Examiner asserts that Scott et al. discusses a method of making pharmaceutical vaccine compositions by combining an antigen with IL-12 and that Fecho discusses that macrophage-derived nitric oxide is involved in depressed ConA responsiveness of splenic lymphocytes and that inclusion of NO synthase inhibitors restores ConA responsiveness.

The Examiner finds that it would be obvious to co-administer IL-12, vaccine antigen, and NO inhibitors while screening the immunostimulatory effect of IL-12 to any vaccine antigen.

Applicants respectfully request reconsideration and withdrawal of this rejection for the following reasons.

The Examiner has asserted that Scott discusses the use of adjuvanting amounts of IL-12 in preparing pharmaceutical compositions, but does not discuss combining IL-12 with a nitric-oxide inhibiting agent and neutralizing agent. Applicants agree.

Further, the Examiner asserts that Fecho suggests the combined effects between cytokines and macrophage derived nitric-oxide synthesis and is therefore related to the use of IL-12 with NO-inhibiting agents and neutralizing agents. Applicants respectfully disagree with this interpretation of Fecho and assert that Fecho has no relevance in combination with Scott.

First, Fecho is not analogous art to Scott, and therefore the combination of these two references is not appropriate. Scott refers to vaccine compositions using IL-12 as an adjuvant. Fecho clearly and repeatedly defines the purpose of its study as investigating the cellular and molecular mechanisms involved in the suppressive effect of *morphine* to rats on the *in vitro* proliferative response of splenic lymphocytes to Con A stimulation. (See, page 5850). Fecho makes no reference to the vaccine field at all. Fecho makes no reference to adjuvants at all. Fecho makes no reference to IL-12, much less any reference to using IL-12 as an adjuvant.

The quotation on page 5851 from Fecho¹ that IL-4, IL-10 and TGF- β inhibit NO synthesis in murine macrophages provides no suggestion relating to the use of NO inhibitors or neutralizing agents with adjuvanting amounts of IL-12. This quotation was, in fact, brought to the examiner's attention to demonstrate that it was a nonsequitur with respect to Scott's teachings. That quotation was noted in the last response for the purposes of directing the examiner's attention to the fact that Fecho says nothing *relevant* about NO inhibitors or NO neutralizing agents in the context of the present invention.

IL-4, IL-10, and TGF- β , are only three of a large number of cytokines known in the art. The generic term "cytokine" defines a large class of compounds, each compound having many different effects on the immune system. What is true about one cytokine is *not* necessarily true about all cytokines. Thus, the fact that IL-4, IL-10, and TGF- β (or, in fact, **any** other compound), inhibit NO synthesis in macrophages as taught by Fecho does not suggest *prima facie* that any other cytokine (or, in fact, **any** other compound) would behave similarly. Thus, Fecho explicitly or implicitly suggests *nothing* about any relationship between IL-12 and NO inhibitors or NO neutralizing agents. Further, since these cytokines mentioned by Fecho were produced in the immunocompetant animal itself, this situation says nothing about the

¹ "For instance, IL-4, IL-10 and TGF- β synergistically inhibit IFN- γ -induced NO synthesis in murine macrophages....The interplay between cytokines in the induction and modulation of NO synthesis by macrophages is being investigated intensively by several laboratories and the findings of future studies promise to clarify this issue."

response of an animal to the exogenous administration of IL-12 as an adjuvant with a vaccine antigen. Fecho is simply not analogous to the present invention.

As Fecho teaches nothing about vaccines or adjuvants and nothing about IL-12, its combination with Scott teaches nothing. There is simply no reason, absent prior knowledge of Applicants' disclosure, for one of skill in the art to combine Scott's vaccine compositions containing IL-12 as an adjuvant with Fecho's irrelevant comments about the suppression of NO synthase by macrophages. The combination of Scott with Fecho does not provide a suggestion to combine any NO inhibiting or neutralizing agents with IL-12 in order to provide a composition useful to adjuvant *any* vaccine antigen.

No combination of IL-12 with NO inhibiting or neutralizing agents is suggested by either of the documents, taken alone or together, for any reason, much less for increasing the adjuvanting ability of IL-12. It is the Applicants who made this inventive suggestion and supported it with enabling disclosure.

The combination of Scott and Fecho fails to supply both the required motivation to combine IL-12 and the NO inhibiting or neutralizing agents, and thus logically provides no reasonable expectation of success. Thus, the combination fails to render the present invention obvious.² As the Examiner knows, obtaining the motivation for combination of the prior art cannot properly be provided by the disclosure.³

Applicants believe that the Examiner is improperly using hindsight to construct the outstanding obviousness rejection by selecting necessary disclosure from the two

² "Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under USC § 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition of device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success." *In re Vaeck*, 947 F. 2d 488, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

³ *In re Oetiker*, 977 F2d 1443, 24 USPQ 2d 1443, 1446 (Fed. Cir. 1992) "There must be some reason, suggestion, or motivation found in the prior art whereby a person of ordinary skill in the field of the invention would make the combination. That knowledge cannot come from the Appellant's invention itself."

references without interpreting the prior art as a whole, from the point of view of a person having ordinary skill in the art at the time the invention was made, as required by 35 USC § 103.⁴ The mere fact that this prior art *may* be modified in the manner as suggested by the examiner does not make the modification obvious, *unless* the prior art suggested the desirability of the modification.⁵ The combination of Scott and Fecho is not a source of such a suggestion. This knowledge is not only absent in the art, but is not suggested in the prior art in combination or taken as a whole⁶.

In view of the above amendments and remarks, Applicants respectfully request that the examiner consider the amended claims and allow them to proceed to issuance in due course.

The Director is hereby authorized to charge any deficiency in any fees due with the filing of this paper or credit any overpayment in any fees to our Deposit Account Number 08-3040.

Respectfully submitted,

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⁴ "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art of deprecate the claimed invention." *In re Fine*, 837 F. 2d 1071, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988).

⁵ *In re Fritch*, 23 USPQ2d 1780, 1783-1784 (Fed. Cir. 1992), citing *In re Gordon*, 221 USPQ 1125, 1127 (Fed. Cir. 1984).

⁶ *Uniroyal Inc. v. Rudkin-Wiley Corp.*, 837 F. 2d 1044, 5 USPQ2d 1434, 1438 (Fed. Cir. 1988) "Something in the prior art as a whole must suggest the desirability, and thus the obviousness, of making the combination."



VERSIONS WITH MARKINGS TO SHOW CHANGES MADE

In the Claims

Amend claims 1, 40 and 41 as follows.

1. (TWICE AMENDED) A method for enhancing the adjuvant effect of IL-12 comprising: co-administering to a mammalian patient said IL-12, a vaccine antigen, and an effective amount of at least one agent selected from the group consisting of a nitric oxide inhibiting agent and a nitric oxide neutralizing agent.

40. (TWICE AMENDED) An adjuvant composition comprising an effective adjuvanting amount of IL-12 and an effective amount of at least one agent selected from the group consisting of a nitric oxide inhibiting agent and a nitric oxide neutralizing agent, in a pharmaceutically acceptable carrier.

41. (TWICE AMENDED) A vaccine composition comprising an effective adjuvanting amount of IL-12, an effective amount of at least one agent selected from the group consisting of a nitric oxide inhibiting agent and a nitric oxide neutralizing agent, and an effective protective amount of a vaccine antigen in a pharmaceutically acceptable carrier.

42. (AMENDED) A method of preparing an adjuvant composition comprising combining in a pharmaceutically acceptable carrier an effective amount of a vaccine antigen, and an effective adjuvanting amount of IL-12 and an effective amount of at least one agent selected from the group consisting of a nitric oxide inhibiting agent and a nitric oxide neutralizing agent.